Claim Rejection under 35 U.S.C. § 112

Claim 33 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner asserted that the phrase "tannin glycoside" has insufficient antecedent basis that renders the claim indefinite. Applicants have deleted the language "tannin" from claim 33 and inserted "lignin". Applicants respectfully submit that this amendment renders the Examiner's rejection moot and request that the Examiner withdraw the rejection.

Applicants have similarly amended claims 32 and 34 to delete the language "tannin" and replace it with "lignin". Such an amendment is appropriate to correct an obvious error, as one of ordinary skill in the art would recognize that the lignin glycoside has properties that include the bonding of lignin and polysaccharide, not tannin and polysaccharide. *See, e.g.,* Tanuma references AB and AC (cited by the Examiner in the Action). The correction of such an obvious error does not constitute new matter because one skilled in the art would recognize that "tannin" was in error and that the appropriate correction should be "lignin". *See In re Oda*, 443 F.2d 1200, 170 U.S.P.Q. 260 (C.C.P.A. 1971); Manual of Patent Examining Procedure ("MPEP"), at § 2163.07.

Claim Rejection under 35 U.S.C. § 103

Claims 26, 27, and 32-34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Tanuma (AB and AC) in view of both Wielckens (BQ) and Wachsman (BO). The Examiner asserted that Tanuma (AB) discloses a lignin glycoside, an inhibitor of poly(ADP-ribose)glycohydrolase, having certain listed properties, that comprises the

structure claimed in claim 33 of the application. The Examiner also states that Tanuma (AC) teaches another lignin glycoside, an inhibitor of poly(ADP-ribose)glycohydrolase, have certain listed properties, useful for treating poly(ADP-ribose)glycohydrolase related diseases. (Action, p. 4.)

The Examiner states that the Tanuma references "do not specifically teach the employment of the lignin glycoside for treating disease directly related to the activity of poly(ADP-ribose)polymerase, e.g., cellular energy depletion, apoptosis, or neurological disorder." (Action, p. 4.) Wachsman, however, the Examiner notes, teaches that inhibitors of poly(ADP-ribose)glycohydrolase retard apoptosis and deplete intracellular NAD, resulting in the depletion of cellular energy. Moreover, Wielckens teaches that the depletion of NAD is caused by drastic stimulation of poly(ADP-ribose)polymerase turnover, which is due to the high activity of both poly(ADP-ribose)polymerase and poly(ADP-ribose)glycohydrolase. (Action, p. 5.)

The Examiner then concluded that it would have been prima facie obvious to a person of ordinary skill in the art to employ the lignin glycosides of Tanuma or the like and the process of Tanuma for treating or preventing diseases or conditions related to apoptosis or for decreasing cellular energy depletion. Applicants respectfully disagree with the Examiner's conclusion and request reconsideration and withdraw of this rejection.

At the outset, Applicants agree with the Examiner that the cited Tanuma references neither disclose nor teach the use of lignin glycoside or the like for treating disease directly related to the activity of poly(ADP-ribose)polymer, e.g., cellular energy depletion, apoptosis, or neurological disorder. As relied on by the Examiner, however,

neither Wachsman and Wielkens disclose or teach the use of lignin glycoside or other PARG inhibitors for inhibiting or decreasing free radical-induced cellular energy depletion in the treatment of diseases related to the activity of poly(ADP-ribose)polymer, e.g., cellular energy depletion, apoptosis, or neurological disorder.

Wielckens emphasizes the importance of mono(ADP-ribosyl) glycohydrolase—not poly(ADP-ribosyl)glycohydrolase ("PARG")—for the drastic stimulation of poly(ADP-ribose) turnover and NAD depletion. Applicants' pending claims 26, 27, and 32-24 pertain solely to poly(ADP-ribose)glycohydrolase. Wielckens summarizes their conclusions regarding mono(ADP-ribosyl), of mono(ADP-ribosyl)glycohydrolase, and poly(ADP-ribosyl)glycohydrolase in the following passages:

> Under the conditions of a high turnover of poly(ADP-ribose), accumulation of nuclear mono(ADP-ribose) groups would be expected if the mono(ADP-ribosyl)glycohydrolase would be the rate-limiting step in the overall turnover of the polymer. This interpretation is consistent with the observation (Fig. 8) that the accumulated mono(ADP-ribosyl) groups exhibit an apparent half-life of 8-10 minutes, which is distinctly longer than that of both fractions of the polymeric ADP-ribosyl groups . . . .
>
> This result is consistent with the interpretation that accumulation of mono(ADP-ribosyl) groups is due to a retarded removal of the primary ADP-ribosyl group from the acceptor protein by a separate mono(ADP-ribosyl) protein glycohydrolase, being the rate-limiting step in the overall turnover of poly(ADP-ribosyl) residues. . . .
>
> Furthermore, at the times of NAD depletion cellular ATP remained unaffected. Activation of NAD glycohydrolase could only be of minor importance, also, since inhibitors of poly(ADP-ribose) synthetase, that have only slight effects on NAD glycohydrolase, still prevent NAD depletion induced by the alkylating cytostatics.

Wielckens, at p. 12876.

Therefore, contrary to the Examiner's conclusion, Wielckens does not teach that the depletion of NAD is caused by "the high activity of both poly(ADP-

ribose)polymerase and poly(ADP-ribose)glycohydrolase." (Action, p. 5). Instead, one of ordinary skill in the art would understand Wielckens as, at best, merely speculating that mono(ADP-ribosyl)glycohydrolase and not poly(ADP-ribosyl)glycohydrolase might be responsible for the high turnover of poly(ADP-ribose), if glycohydrolase is of any importance at all with respect to cellular energy depletion. One of skill in the art would not reasonably expect that poly(ADP-ribosyl)glycohydrolase is responsible for the high turnover of poly(ADP-ribose) when Wielckens et al. actually teaches away from this conclusion.

Moreover, Applicants' pending claims are primarily directed to a method for inhibiting or decreasing free radical-induced cellular energy depletion, cell death, or cell damage by treatment with a poly(ADP-ribose)glycohydrolase inhibitor. See, e.g., claims 26 and 27. Wielckens does not disclose or teach the use of PARG inhibitors to treat or prevent tissue damage from free-radical-induced cellular energy depletion, cell death, or cell damage.

Applicants note that there are many enzymes, e.g. poly(ADP-ribose) glycohydrolase (PARG), mono-ADP-ribosyl glycohydrolase, and phosphodiesterase, which are potentially involved in degrading poly(ADP-ribose). While the references cited by the Examiner suggest that poly(ADP-ribose)polymerase (PARP) activation contributes to NAD depletion, it is only speculative that poly(ADP-ribose) degradation may also contribute to NAD depletion. Furthermore, as demonstrated by the conclusions drawn in Wielckens, it was not at all established whether it was poly(ADP-ribose)glycohydrolase, mono-ADP-ribosyl glycohydrolase, or other enzymes that play a major role in lowering NAD.

As for Wachsman, the Examiner has cited this article for the proposition that it "teaches that inhibitors of poly(ADP-ribose)glycohydrolase will retard apoptosis." (Action, p. 5.) Applicants respectfully disagree. The Examiner's interpretation of Wachsman simply does not cure the deficiencies of Wielckens and Tanuma. When read as a whole, one of ordinary skill in the art would not understand Wachsman to suggest with a reasonable expectation of success that inhibitors of poly(ADP-ribose)glycohydrolase *will retard apoptosis*. A prior art reference must be considered in its entirety, as a whole invention, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.P.S.Q. 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

When read as a whole, Wachsman does no more than offer an unsubstantiated guess that poly(ADP-ribose)glycohydrolase might—along with other enzymes—retard apoptosis. Such a view is plainly evident by the following statements:

> The steady-state level of poly(ADP-ribose), ..., is strongly influenced by the intracellular NAD concentration, as well as by the activities of poly(ADP-ribose) glycohydrolase *and other enzymes involved in polymer degradation. Little is know[n] (sic) about the glycohydrolase* . . . . (Emphasis added.)
>
> *It would be of considerable interest* to determine how polymer level varies during the process of apoptosis *and to see if glycohydrolase inhibitors* retard apoptosis. (Emphasis added.)
>
> In addition, CR [calorie restriction] could increase apoptosis by modulating PARP activity by decreasing the level of poly(ADP-ribose) and by enhancing the formation of GJIC. This proposal, as well as the effect of CR on the activities of PARP, the glycohydrolase, and the PARP-specific protease *should be tested* in animal systems. Consistent with this *model is the prediction* that chemical inhibitors of the glycohydrolase or of the PARP-specific protease should retard the process of apoptosis and accelerate carcinogenesis. (Emphasis added.)

Wachsman, at pp. 29-30, 32.

These quotes demonstrate that the authors of Wachsman simply *propose* that *as a model* (Wachsman, p. 32), it would be interesting to see how calorie restriction affects the levels of poly(ADP-ribose)polymerase, poly(ADP-ribose), poly(ADP-ribose)glycohydrolase and other enzymes. There is no experimental data or specific guidance in Wachsman to support its guess that a chemical inhibitor of poly(ADP-ribose)glycohydrolase might retard apoptosis. While Wachsman might suggest experimenting with chemical inhibitors of poly(ADP-ribose)glycohydrolase, the authors have many reservations about the outcome and are quite skeptical about their predictions. Indeed, as evidenced by their cautionary statement above, the authors are not sure how many or what enyzmes may affect the "steady-state level of poly(ADP-ribose)."

Undeniably, the primary and most-developed approach in Wachsman involves the actions of PARP—not PARG. Even the actions of PARP, however, defy explanation as noted below:

> It seems reasonable to expect that under appropriate experimental conditions, inhibitors of PARP activity would . . . accelerate the process of apoptosis. Indeed, studies have shown [this] . . . . Other studies, however, have shown the PARP inhibitors can delay apoptosis. The reasons for these apparently contradictory results are complex . . . . (Wachsman, at p. 30.)

Those skilled in the art would not reasonably expect PARG inhibitors to retard apoptosis given that the same proposition for PARP has already demonstrated contradicting results.

Given these reservations by the authors of Wachsman, those skilled in the art would hardly have a reasonable expectation of success that an inhibitor of poly(ADP-ribose)glycohydrolase would decrease free radical-induced cellular energy depletion, cell death, or cell damage as claimed in the applicants' invention. While obviousness does

not require absolute predictability, at least some degree of predictability is required. MPEP § 2143.02. Wachsman unsubstantiated guesses regarding the action and effect of PARG inhibitors does not demonstrate a reasonable level of predictability.

Furthermore, the Examiner's use of Wachsman in this fashion appears to utilize the impermissible "obvious to try" standard under Section 103. MPEP § 2145(X)(B) explains one of the two common scenarios where the "obvious to try" standard is mistakenly employed:

> In others [where an "obvious to try" standard is error], what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Wachsman, at most, offers a hypothetical general approach—without actual experimentation—replete with speculation concerning what it expressly states is a new technology ("little is known about the glycohydrolase"). Such reliance on Wachsman impermissibly applies the "obvious to try" standard.

For the reasons given above, one of skill in the art would not consider the claimed invention prima facie obvious. A person or ordinary skill in the art would not be motivated to employ Tanuma's lignin glycosides or the like for treating or preventing diseases or conditions related to apoptosis or for decreasing cellular energy depletion as purportedly taught by Wielckens and/or Wachsman. Wielckens et al. emphasized the importance of mono(ADP-ribosyl)glycohydrolase—not poly(ADP-ribosyl)glycohydrolase—for the drastic stimulation of poly(ADP-ribose) turnover and NAD depletion. Wachsman merely suggests experimentation with PARG inhibitors—a

new field to explore for its interesting comparisons and contradictions with the better-known but as yet not fully understood PARP inhibitors.

Considered together, those skilled in the art at the time the invention was made would not be motivated to employ Tanuma's lignin glycosides as PARG inhibitors to inhibit or decrease free radical-induced cellular energy depletion, cell death, or cell damage as claimed in applicants' invention. Similarly, those skilled in the art would not be motivated to employ Tanuma's lignin glycosides as PARG inhibitors to treat or prevent diseases or conditions as claimed in claim 32. Applicants respectfully request that the Examiner withdraw this rejection.

In view of the foregoing amendments and remarks, Applicants submit that there is no basis for applying the previous rejections to the pending claims and withdrawal of the rejections is respectfully requested. Accordingly, the claims are in condition for immediate allowance and Applicants earnestly solicit from the Examiner early notice of such favorable action.

Should the Examiner have any questions or believe a personal or telephonic interview may be in order, the Examiner is invited to contact the undersigned at her earliest convenience.

The Commissioner is hereby authorized to charge any additional fees (or credit any overpayment) associated with this communication to the Deposit Account No. 50-0622.

Respectfully submitted,

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